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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,464	FEUSSNER ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/EP00/06539.

Claims 12-28 are pending. Claims 24-28 are withdrawn. Claims 12-23 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on February 10, 2005, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 22-23 are rejected under 35 U.S.C. 101 because the claimed invention is directed to a non-statutory subject matter.

Claims 22-23, as written, do not sufficiently distinguish over a cell as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products, such as being "transformed" with the vector of claim 18 or being a "recombinant host cell". In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193

(1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "transformed" as taught by the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16-17 recite the phrase "obtainable". A polypeptide that is "obtainable" conveys that the polypeptide is obtained under some conditions but may be obtained under all or other conditions. A polypeptide that is "obtainable" may not be obtained at all times. Therefore, it is not clear what are those conditions in which the polypeptide is "obtainable" as recited in the above claims. Examiner requests clarification of the above phrase and suggests amending it to "obtained from" to render the claim definite.

Claim 12 and claims 13-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 12, applicants have recited an accession number from the EMBL database. It is impossible for the Exmainer t odo a meaningful search without the actual

sequence for the enzyme. Further more, since the database accession numbers are bound to change, Examiner suggest providing a SEQ ID number for the encoded enzyme. It is also unclear to the Examiner to which residue position 576 corresponds to the lipoxygenase having accession number S73865 in the EMBL database since the amino acid sequence of S73865 can be deleted or altered. Also, it is unclear as to how those skilled in the art can identify as to which residue position corresponds to position 576 claimed herein in any plant lipoxygenase since a definite sequence for any or all plant lipoxygenase is not identified by an amino acid sequence.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that amendment of claim 12 to recite S73865 in the EMBL database in order to reference the amino acid sequence of a potato tuber lipoxygenase has overcome the rejection. Examiner respectfully disagrees. Without the actual sequence, Examiner will be unable to do a meaningful search and Examiner has no means to import the sequence from EMBL database in order to do a search. Furthermore, a sequence in an EMBL database can be altered or deleted and therefore would become unavailable. Therefore, the recitation of an accession number for the sequence for a potato tuber lipoxygenase does not make the claim definite. Hence, the rejection has been maintained.

Claim 12 and claims 13-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 12, the phrase "corresponding to " is not clear. The metes and bounds are not clear in the context of the claims. The specification does not describe as to how one skilled in the art can determine as to which specific amino acid in a given lipoxygenase protein "corresponds" to the amino acid at position 576 claimed herein. Therefore, it is unclear from the specification or from the claims as to what applicants mean by the above phrase. Examiner suggests direct reference to the amino acid position.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12-23 are drawn to a method enhancing the specificity of a plant lipoxygenase by substituting residue 576 of any plant lipoxygenase, a lipoxygenase variant obtained by said method, a polynucleotide encoding said variant, and a vector and host cell comprising said polynucleotide. The claims encompass a method of enhancing the specificity of any plant lipoxygenase, any plant lipoxygenase having a substitution at position 576 and polynucleotides encoding any plant lipoxygenase having a substitution at position 576. Therefore, the claims are drawn to a method of

enhancing substrate specificity of a genus of plant lipoxygenases, including variants, recombinants and mutants, a genus of polypeptides comprising recombinant, variant and mutant of any plant lipoxygenase having any structure except for the specific amino acid position at 576, a genus of polynucleotides encoding said recombinants, variants and mutants. The specification only describes a method of increasing specificity towards position 11 of arachidonic acid by modifying a potato tuber 5-lipoxygenase with a substitution at position 576, a potato tuber 5-lipoxygenase comprising a substitution at position 576 and a polynucleotide encoding said mutant. However, these examples are not enough to describe the structure and more importantly do not constitute a representative number of species to describe the whole genus and there is no evidence on the record of the relationship between the structure of the claimed variant and the structure of any recombinants, variants and mutants of a lipoxygenase from any plant source. Therefore, the specification fails to describe the structure of species of a genus comprising a method of enhancing the specificity of any plant lipoxygenase, a genus comprising any plant lipoxygenase substituted at position 576 or a genus comprising a polynucleotide encoding any plant lipoxygenase substituted at position 576.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 12-23.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that one species can be enough to support a genus when it conveys to the ordinarily skilled artisan the necessary common attributes possessed by the genus. Examiner respectfully disagrees. The claims are not only drawn to mutant lipoxygenase having a mutation at a position corresponding to residue 576 of a potato tuber lipoxygenase with accession number S73865 in the EMBL database, but to any or all mutants, variants and recombinants of any plant lipoxygenase. The genus comprising any or all recombinants, variants and mutants of any plant lipoxygenase does not possess any common attributes other than having lipoxygenase activity. Therefore, the specification lacks description of a representative number of species to describe the whole genus.

Applicants also argue that more than one species is taught since the specification describes different plant lipoxygenases and one having ordinary skill in the art would recognize to use these plant lipoxygenase and mutagenize the residue corresponding to position 576. Examiner respectfully disagrees. As discussed above, the claims are not only drawn to mutant lipoxygenase having a mutation at a position corresponding to residue 576 of a potato tuber lipoxygenase, but to any or all mutants, variants and recombinants of any plant lipoxygenase. Therefore, the specification

lacks description of a representative number of species to describe the whole genus. Hence the rejection is maintained.

Claims 12-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing specificity of a potato tuber 5-lipoxygenase towards position 11 of arachidonic acid variant by substituting position 576, a potato tuber 5-lipoxygenase variant substituted at position 576 and a polynucleotide encoding said potato tuber 5-lipoxygenase variant, does not reasonably provide enablement for a method of enhancing specificity of any plant lipoxygenase, any plant lipoxygenase variant comprising a substitution at position 576 or a polynucleotide encoding any plant lipoxygenase variant comprising a substitution at position 576. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 12-23 are drawn to a method enhancing the specificity of a plant lipoxygenase by substituting residue 576 of any plant lipoxygenase, plant lipoxygenase variant comprising an amino acid substitution at position 576, a polynucleotide encoding said variant, and a vector and host cell comprising said polynucleotide. The claims encompass a method of enhancing the specificity of any plant lipoxygenase, any recombinants, variants and mutants of any plant lipoxygenase having an substitution at position 576 and a polynucleotide encoding any recombinants, variants and mutants of any plant lipoxygenase having an substitution at position 576. Therefore, the claims are drawn to a method of enhancing substrate specificity of any plant lipoxygenase having any structure, including variants, recombinants and mutants, any plant lipoxygenase variants comprising a substitution at position 576 and a polynucleotide encoding any plant lipoxygenase variant comprising a substitution at position 576.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides and polypeptides encompassed by the claims. Since the encoded amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method of increasing specificity towards position 11 of arachidonic acid by

modifying a potato tuber 5-lipoxygenase with a substitution at position 576, a potato tuber 5-lipoxygenase comprising a substitution at position 576 and a polynucleotide encoding said mutant.

It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides and polypeptides and enhance specificity of any plant lipoxygenase. The specification provides no guidance with regard to the making of other variants and mutants or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides and polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides and polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claim, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any plant lipoxygenases and polynucleotides encoding any plant lipoxygenase, including variants and mutants because the specification does not establish: (A) regions of the polypeptide structure, other than the substitution recited in the claims, which may be modified without affecting lipoxygenase activity or 5-lipoxygenase activity; (B) regions of the polypeptide structure which may be modified resulting in enhanced substrate specificity towards position 11 of arachidonic acid; (C) the general tolerance of lipoxygenase to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of enhancing specificity of any plant lipoxygenase, any plant lipoxygenase variant comprising a substitution at position 576 and a polynucleotide encoding any plant lipoxygenase variant comprising a substitution at position 576. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides comprising any variants, mutants and recombinants of plant lipoxygenase having enhanced substrate specificity is unpredictable and the experimentation left to those skilled in the art is unnecessarily,

and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the specification teaches the structure of various plant lipoxygenase and therefore a person skilled in the art has sufficient guide in making mutant lipoxygenases. Examiner respectfully disagrees. Even though the structure of some wild type lipoxygenase are taught, the claims are not only drawn to mutant lipoxygenase having a mutation at a position corresponding to residue 576 of a potato tuber lipoxygenase with accession number S73865 in the EMBL database, but to any or all mutants, variants and recombinants of any plant lipoxygenase. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. While the art may teach in general the structure of lipoxygenases, conserved amino acid sequences, and etc, such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art. Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gan et al., Sloane et al. and Geerts et al.

Claims 12-23 are drawn to a method of enhancing a plant lipoxygenase towards position 11 of arachidonic acid by substituting the residue at 576, a plant lipoxygenase variant comprising a substitution corresponding to position 576 and a polynucleotide encoding said variant. Examiner notes that the patentability of a product does not depend on the method used in producing the product (MPEP 2113).

Gan et al. (form PTO-892) discloses that Phe at position 557 of a soybean 1-lipoxygenase and Met at position 418 of a human lipoxygenase are critical for substrate binding and effects positional specificity of arachidonic acid (abstract, pages 25412-

25413). Sloane et al. (form PTO-892) discloses site directed mutagenesis at position 418 of human lipoxygenase changes the enzyme's substrate specificity. A sequence alignment of Accession number S73865 and the sequences of Sloane et al. and Gan et al. shows that amino acid 418 of human lipoxygenase and amino acid 557 of soybean lipoxygenase, correspond to position 576 of a potato tuber 5-lipoxygenase (See sequence alignment).

The difference between the references of Gan et al. and Sloan et al. and the instant invention is that the references do not teach a method of enhancing the specificity of a potato tuber lipoxygenase for position 11 of arachidonic acid by substituting residue 576 with a Phe residue, or a potato tuber lipoxygenase variant comprising a substitution at residue 576 or a polynucleotide encoding said variant.

Geerts et al. (form PTO-892) discloses a polynucleotide encoding a potato tuber 5-lipoxygenase having an accession number S73865 in the EMBL database (page 272). Gerets et al. also discloses a vector and host cell comprising said polynucleotide (page 270).

Therefore, combining the teachings of the above three references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to mutagenize the lipoxygenase of Geerts et al. at position 576. One of ordinary skill in the art would have been motivated to mutagenize the lipoxygenase of Geerts et al. in order to alter the enzyme's positional specificity of arachidonic acid. One of ordinary skill in the art would have had a reasonable expectation of enhancing the enzyme's positional specificity of position 11 of arachidonic acid since Gan et al. and

Sloane et al. teach that the residue corresponding to position 576 of potato tuber lipoxygenase is critical for substrate binding and effects positional specificity of arachidonic acid.

Therefore, Gan et al., Geerts et al. and Sloane et al. render claims 12-23 *prima facie* obvious to those skilled in the art.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Examiner 1652